1920
W52

R. W. Westermann

Various Esters of Para Amino Benzoic Acid

VARIOUS ESTERS OF PARA AMINO BENZOIC ACID

BY

RICHARD WILBUR WESTERMANN

THESIS

FOR THE

DEGREE OF BACHELOR OF SCIENCE

IN

CHEMICAL ENGINEERING

COLLEGE OF LIBERAL ARTS AND SCIENCES

UNIVERSITY OF ILLINOIS

1920

1920
W52

UNIVERSITY OF ILLINOIS

June 2, 1920

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

RICHARD WILBUR WESTERMANN

ENTITLED VARIOUS ESTERS OF

PARA AMINO BENZOIC ACID.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF BACHELOR OF SCIENCE IN CHEMICAL ENGINEERING

Roger Adams

Instructor in Charge

APPROVED: W. A. Noyes

HEAD OF DEPARTMENT OF CHEMISTRY.

458820

UIUC

CONTENTS

page.

I. Introduction - - - - - - - - - - 1-2.
Commercial esters of para amino benzoic acid, Purpose of work, Quantities and uses of esters made.

II. Historical - - - - - - - - - - - 3-6.
Anaesthetics in general, Local anaesthetics, Ester of para amino bezoic acid.

III. Theoretical - - - - - - - - - - 7-10.
Chemical constitution and anaesthetic action, Effect of groups and side chains.

IV. Experimental - - - - - - - - - 11-19.
A. Outline of work. Laboratory preparation, Anaesthetic action, General methods, Special methods.
B. Laboratory work and Syntheses. Methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-amyl, isoamyl.

V. Summary and Conclusions - - - 20-23.
Methods, Anaesthetic value of esters, Table of properties, Physical relations.

VI. Bibliography- - - - - - - - - - 24-25.
Books, Periodicals, Patents.

Acknowledgment - - - - - - - - - - 26.

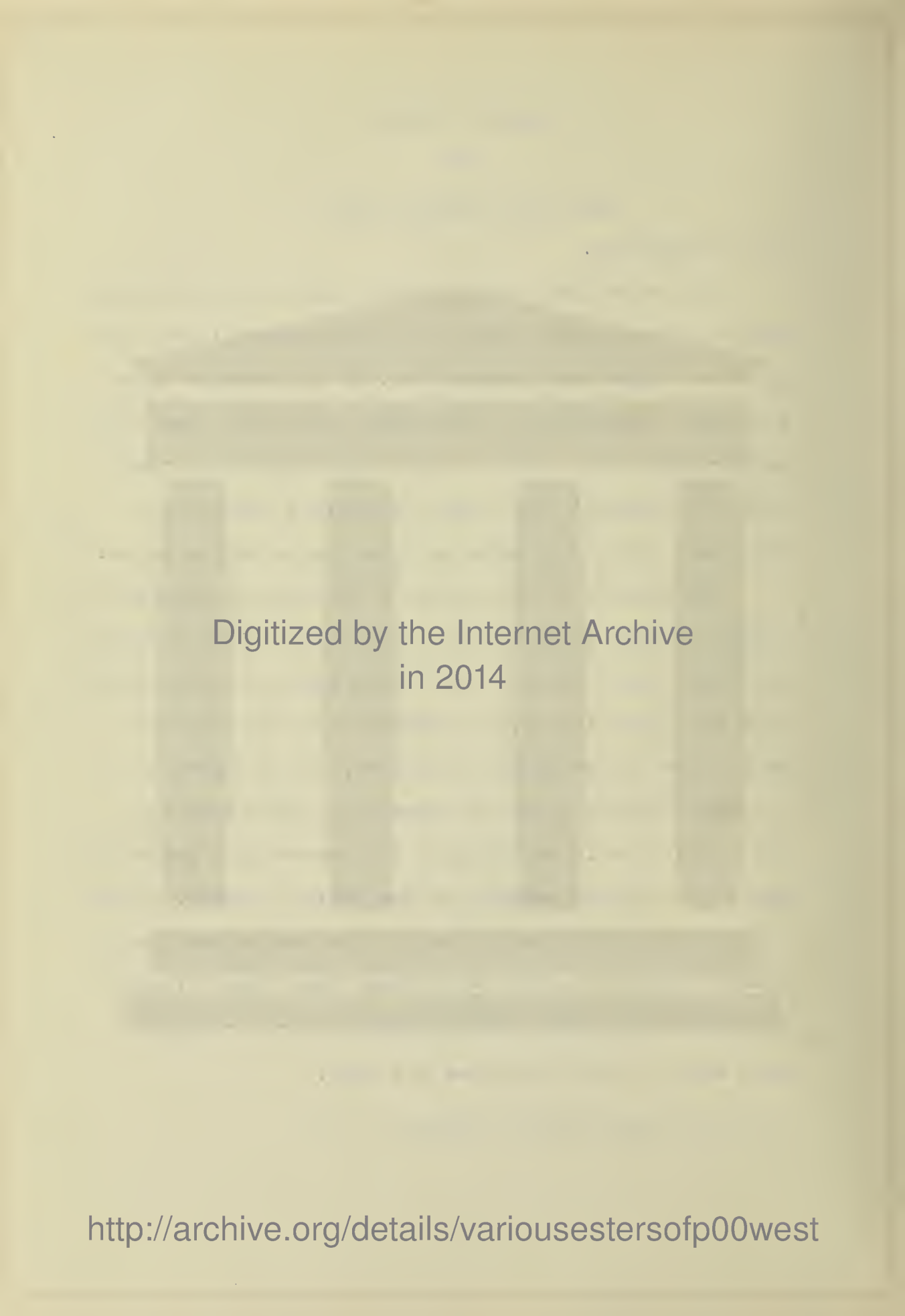
VARIOUS ESTERS
OF
PARA AMINO BENZOIC ACID

I. Introduction.

The anaesthetic value of the esters of para amino benzoic acid is well known. The ethyl ester is the one that has found most general use. It is marketed under the name "Anaesthesin". The propyl ester has been made, commercially, and used to some extent under its trade name, "Propaesin". Some other aliphatic esters have been made and their value as local anaesthetics noted.(1)*

The purpose of the author's work was to prepare the esters of para amino benzoic acid with various aliphatic alcohols, particularly those which have not been studied thus far. From the series prepared and the relative properties of the separate members, it was hoped that some conclusions could be drawn as to the cause for the difference in strength of the anaesthetic properties which the various members of the series possess. It was also hoped to find out if any of the new members would possess properties that would make them more valuable as anaesthetics than the ones now in use, or suggest some way of improving those now used.

(1)* See bibliography, page 24.


Digitized by the Internet Archive
in 2014

http://archive.org/details/variousestersofp00west

The esters were made in such quantities that determinations could be made of all the physical constants and still have enough for the other purposes. The relative anaesthetic strength was tested by puttin a small ammount of each on the tip of the tongue. Some was also wanted for the experimental work of a doctor who was to test out the anaesthetics in a practical way. A small ammount was needed for making determinations of the surface tension and of the partition coefficient, the latter to get some idea of the probable toxicity.

II. Historical.

J. L. Corning[1] says in his book on local aneasthesia, " With all our progress --------- we yet stand on the brink of misery. ------ It is but natural that, failing to eliminate the causes of suffering, man should have attempted to exorcise pain by occult spells or by more cunning ideas. Anaesthesia is the outgrowth of this idea.

The oldest Assyrians alleviated pain by compression of veins in the neck. The soporific properties of opium and Indian hemp have been known for countless ages. The Egyptians, Chinese, and natives of India knew the sleep-producing properties of various substances. The more recent developments in modern anaesthesia are the use of nitrous oxide (Sir Humphry Davy; 1799) and ether (Dr. W. C. Long; 1842).

The first most extensive work on local anaesthetics was done by Dr. H. H. Beggs[7] in which cocain was the local anaesthetic tested. A search for new local anaesthetics which would substitute cocain or offer improvements over it has been carried on ever since the advent of synthetic organic chemistry with the result that there are now numerous synthetic anaesthetics, which in turn has led to investigations of the relative properties and the cause of the anaesthetic action and a search for still more anaesthetics.

Considerable study has already been made of the esters of para amino benzoic acid. Patents in Germany, Great Britain, and the United States have been taken out for several of these esters.(20-29) A few are on the market under the trade names:

Methyl ester of para amino benzoic acid--Orthoform
Ethyl " " " " " " - Anaesthesin
Propyl " " " " " " - Propaesin
Isobutyl " " " " " " - Cycloform

The most important paper on the relative value of the esters is by two German doctors, Stürmers and Lüders.(18) The esters tested were the methyl, ethyl, normal propyl, iso propyl, and isobutyl which were found to have different anaesthetic properties and difference in solubility, the higher members being less soluble. The conclusion drawn was that the normal propyl ester was the most satisfactory. The isoamyl ester was found to act very strongly but it was irritating.The anaesthetic value seems to increase with the size of the esterifying group but this is compensated by the decrease in solubility, the propyl ester being midway is the most practical.

The patent claims for the various esters concede the propyl ester to be the best for use.

The methyl ester was first made and described by Einhorn and Oppenheimer(11) in a paper on new anaesthetics. The method and properties are given in Beilstein(5)

The ethyl ester was first made by H. Salkowski [17] in a work on the esterification of aromatic amino acids. This ester had never been described in the literature before and so he gives the method he employed in making it. Hydrochloric acid was passed thru a solution of para amino benzoic acid in ethyl alcohol. The hydrochloride forms in fine needles. The free ester is obtained by neutralizing with soda solution, separating in needles, M.P. 89-90° C.

The ethyl ester is also described in a paper by Vorlander and Meyer[19] on aromatic diazoniums and in another paper by Limpricht and Sarr.[13] The method used in the latter case was the formation of the ester of para nitro benzoic acid and subsequent reduction with ammonium sulfide.

The normal propyl ester was first described in a German patent.[20] The patent was taken for all methods as; preparation by direct esterification of alcohol and acid with hydrochloric acid gas or with sulphuric acid, and the preparation of the ester of para nitro benzoic acid and reduction.

The isopropyl ester has been covered by patents in Germany and Great Britain.[21, 22]

The isobutyl ester is the only one of the esters of the butyl alcohols that is described in the literature. The various methods given in the patent[23] are;

direct esterification of para amino benzoic acid with isobutyl alcohol by passing in the mixture dry hydrochloric acid; esterification of para nitro benzoic acid by the same method, followed by reduction with stannous chloride; esterification of benzoic acid azo beta napthol with isobutyl alcohol and reduction with stannous chloride; esterification of the salt of the acid with isobutyl bromide in the manner given: Make a solution of para amino benzoic acid in isobutyl alcohol, add sodium dissolved in isobutyl alcohol, then add isobutyl bromide and reflux for twenty hours, distill off the alcohol and extract the ester with ether.

The esters of the amyl alcohols could not be found in the literature, except that mention is made in one[18] case of the use of isoamyl para amino benzoate but nothing is said about its preparation, properties, or physical constants.

III. Theoretical.

All aromatic compounds have anaesthetic properties to some degree. Speigel[4] in his book, "Chemical Constitution and Physiological Action" presents some interesting ideas and conclusions on the subject. His work, founded on a similar work by Fränkel[2] is to systematize the many facts and discoveries pertaining to poisons, anaesthetics, disinfectants, and other compounds of therapeutic interest. He puts these compounds into inorganic and organic divisions. The organic division includes the aliphatic, aromatic, and nitrogen compounds. His discussion shows that the nitrogen compounds constitute a large part of the compounds of therapeutic interest. The esters of para amino benzoic acid are classed with the amines, along with atropine and cocain.

There are certain groupings that furnish the preliminary basis for certain effects. It has also been observed that, given these fundamental nucleii, the physiological action of the compound may be varied, either weakened or strengthened, by the introduction of side chains. Among these side chains which seem to release the latent action of the nucleus there are those groups which favor an increased chemical activity. This is strikingly noticeable in the amino, hydroxyl, and carboxyl groups, in fact these groups are so

powerful in this manner that it is frequently necessary to introduce other groups that will have a weakening effect before the compound is suitable for safe and reliable therapeutic use. Such weakening effect may be brought about in amino bodies by the introduction of an acid constituent. A possibility to be guarded against is the carrying of the weakening effect so far as to destroy the action entirely. Such is the case very often with carboxylic and even more often with sulphonic acids. This is easily understood from a chemical standpoint because a strongly acid group is introduced into a basic compound.

The effect of the side chain is very often altered by altering the side chain. For example, in the esterification of para amino benzoic acid, if propyl alcohol is used instead of ethyl, the "Propaesin" formed has a stronger anaesthetic action than the "Anaesthesin" from the ethyl alcohol.

The effect of the side chain is not always due to the side chain itself but because the side chain covers up some effect that interferes with the desired action. An ester of an acid with a longer esterifying group may have a stronger action, not because of the side chain directly but because the longer chain more completely obscures some conflicting effect.

It was found that nearly all the esters of amino-oxy- benzoic acid have local anaesthetic action.[9] The compounds were difficultly soluble but had espacial effect on exposed nerve ends. Later it was discovered that the hydroxyl group on the ring was not a necessary requisite for anaesthetic action. Rissert[16] recommended in 1902 the use of the ethyl ester of para amino benzoic acid. Still later Impens[15] recommends the isobutyl ester "Cycloform" and in the same paper claims that the amyl and benzyl esters have even greater effect. This is an example of greater activity with increase of carbon atoms in the side chain. The difficulty with the use of long chains is the decrease in solubility. Spcigel[4] states that because of the slight solubility of the esters of para amino benzoic acid their use has been limited largely to external applications, as on open cuts and wounds. They have this limitation because of the low solubility in the liquids ordinarily used for injections. The hydrochloride of the amines are soluble but so astringent, due to the acid, that they cannot be used. One practical application of the free ester comes in denistry where the gums can be dusted before and after the extraction of a tooth. The action is that of deadening the nerve ends.

It is interesting to note that two substances having anaesthetic value of themselves, as para amino benzoic

acid and menthol when combined by esterification, have practically no anaesthetic properties.

IV. Experimental

A. Outline of the work.

To determine the action of the esters of para amino benzoic acid it was decided to vary the esterifying alcohol and note the action of the ester when different side chains were attached to the carboxyl group. By varying this one factor it was hoped that a definite conclusion could be reached as to the cause of the anaesthetic action and the effect of the size of the side chain on this specific compound at least.

The esters for which references were found were the methyl, ethyl, normal propyl, isopropyl, and the isobutyl.

The plan for the laboratory work of synthesis was to make the known esters by the most suitable methods given in the literature, and then decide which would be the best for the preparation of the esters which had not been made. Thus the whole series of known and new esters would be at hand to get the relative anaesthetic value and other properties.

After the series had been completed the relative value of the esters was tested by putting a small amount on the tongue and noting the comparative anaesthetic properties of the different members. The toxicity of the esters can only be judged by a con-

sideration of the taste and action on the tongue and the local after-effects. Determinations were to be made later of the partition coefficient with oil to get a more definite idea of the toxicity. Dr. Rideal was to test the surface tension of the products to get some data from which the anaesthetic value might be learned. The esters were to be tested in a practical way by a practicing physician.

The general methods for the esterification of acids with aliphatic alcohols are:

1. acid refluxed with alcohol -inorganic acid-
2. acid with alkyl chloride
3. acid chloride with alcohol
4. salt of acid with alkyl chloride
5. acid chloride with metalic alcoholate.

None but the first are satisfactory for amino acids.

The most practical way for the synthesis of esters of amino acids is to esterify the nitro or azo compound corresponding,and reduce this ester to the amine. Esterification of para nitro benzoic acid can be carried out by any of the above methods. The first method goes very well with the alcohols of low molecular weight. The third was chosen as being best for the higher alcohols.

The general methods for reduction of nitro compounds are the use of hydrogen formed by the action of metals on water, acid or alkali, stannous salts, sulfides, and oxidizable organic compounds. The reduction of nitro compounds with iron and water in the presence of a

small ammount of hydrochloric acid usually is very satisfactory and seemed to be the best one to use.

The general methods given above were typical of the methods given in the literature and patents. The methods given for the synthesis of the various known esters are given in the following.

The methyl ester of para amino benzoic acid [11] [12] was first prepared by passing dry hydrochloric acid into a solution of para amino benzoic acid in methyl alcohol, refluxing for six hours. The ester was freed from the hydrochloric acid salt and recrystallized from dilute methyl alcohol.

The literature for the ethyl ester is most abundant of all.[17] [19] [13] [5] The method first used by Salkowski[17] was the same as that given for the methyl ester[11] above except that ethyl alcohol was used.

The method given for the normal propyl ester in the German patent[20] is the esterification of para nitrobenzoic acid with normal propyl alcohol in the presence of considerable sulphuric acid. The ester of the nitro compound is reduced with tin and hydrochloric acid to the amine. The method used for the methyl ester[11] is also given.

Four methods are given in the patent[21] for the isopropyl ester. First, esterification as given for the methyl.[11] Second, esterification of para nitro

benzoic acid by the same method and then reducing this ester. Third, by the use of benzoic acid azo beta naphthol for esterification, and then reducing. Fourth, by the use of the action of isopropyl iodide on the sodium salt of para amino benzoic acid and refluxing in a solution of isopropyl alcohol for twenty hours.

The isobutyl ester[23] is described in the patent for it as being made by the same methods given for the ester of isopropyl alcohol.

B. Laboratory Work and Syntheses.

The esterification of the alcohols and para nitro benzoic acid and subsequent reduction with powdered iron was considered the most practical way to make the esters. Direct esterification was made with methyl alcohol and para nitro benzoic acid in the presence of a small amount of hydrochloric acid to act as a catalyst. This method was not practical for the higher alcohols and so esterification was accomplished by making para nitro benzoyl chloride and condensing with the alcohol. In cases where the alcohol was scarce, just theoretical amounts of the alcohol and benzoyl chloride were refluxed.

The reduction in every case was carried out by the use of powdered iron and water with a little hydrochloric acid. Very good results were obtained by this method.

The results in the case of each individual ester are given below.

The methyl ester was made by refluxing for six hours in a liter flask,107 grams of para nitro benzoic acid with 500cc of methyl alcohol. By this time there was no solid left undissolved in the hot alcohol. The excess of methyl alcohol was distilled off and the residue shaken with sodium carbonate solution. 150 grams of methyl para nitro benzoate were obtained and 12 grams of para nitro benzoic acid recovered from the sodium carbonate solution. The yield, based on acid used,was 81%.

The reduction was carried out by putting 24 grams of methyl para nitro benzoate in a beaker, adding 160 grams of powdered iron and then water until a thin paste was made. A few cc of hydrochloric acid were added and the mixture stirred with a glass rod stirrer having a pulley driven by a small motor. The heat of reaction evaporated some of the water which was replaced by more and the beaker heated on a water bath for about an hour longer with continued stirring. The resulting mass was cooled, keeping it stirred with sufficient water to prevent caking, and then shaken with several of ether portions equal to the ammount of solid. Sodium carbonate was added and the residue shaken and extracted twice more with ether. These ether extracts were filtered and then the ether distilled off, leaving the amine as a brownish residue. The yield of the reduction was about 90%. The amine was purified by recrystallization from dilute methyl alcohol.

The ethyl ester of para amino benzoic acid was available as a commercial product and so was not prepared.

The normal propyl ester was made by refluxing 40 grams of para nitro benzoyl chloride with an excess of normal propyl alcohol for six hours. The normal propyl alcohol was distilled off and the ester distilled under reduced pressure of 15mm. The reduction was made in the same way as given for the methyl ester except that a little alcohol was added to increase the solubility and make the reduction go more quickly. The impure amine after the ether was distilled off was purified by recrystallization from ligroin. A pure sample of the normal propyl para nitro benzoate was gotten by recrystallization from hot alcohol, from which it separated in flat yellow plates.

The isopropyl ester of para amino benzoic acid was made by using the same proceedure gone thru for the normal propyl ester. Not much difference was noticed between the two.

The normal butyl ester had been made by Dr. Adams and as some was on hand, the melting point was determined and the anaesthetic properties noted.

The isobutyl ester was made for the author by Mr. W. E. Baus by refluxing para nitro benzoyl chloride with an excess of isobutyl alcohol, distilling off the excess of alcohol, then distilling the ester under reduced pressure of 15mm, and reducing the nitro compound with iron,as given for the methyl ester. The amine could

not be purified satisfactorily by recrystallization from ligroin and so the sulphuric acid salt was made which could be recrystallized very well from hot water. The amine was freed with sodium carbonate and crystallized from ligroin.

The normal ester was made by refluxing 102 grams of para nitro benzoyl chloride with the theoretical amount, 48 g., of normal alcohol for esterification. The resulting ester was distilled under reduced pressure of 45mm, distilling at atemperature from 232-234°C. The yield was 94g of a yellow liquid, yield,74% of the alcohol. The reduction of the oily nitro compound with powdered iron went very well, giving the amine, which ,when recrystallized from ligroin melted at 53°C.

The isoamyl alcohol could be obtained in considerable quantities and so the ester was made by using para nitro benzoyl chloride and an excess of the alcohol as given for the propyl alcohols above. The reduction was made by the use of powdered iron with good results. As large an excess of iron as before was not used, however, and the nitro compound was ground in a mortar with the iron to get very intimate contact. This seemed to make the reduction go better.

The para nitro benzoic acid ester was a liquid at room temperature but froze at 12°C. The isoamyl para amino benzoate is a solid similar to the normal amyl compound.

In the synthesis of most of the esters, para nitro benzoyl chloride was used. To make the large amounts of this compound needed, a new method was worked out. The ordinary method, used for the first two preparations, was to mix the theoretical amounts of para nitro benzoic acid and phosphorous pentachloride, warm, distill off the phosphorous oxychloride, and then distill the para nitro benzoyl chloride under reduced pressure. The product obtained by this method melted three degrees low and had the strong odor of phosphorous oxychloride, even after the distillation.

It was learned that para nitro benzoyl chloride did not hydrolize rapidly in water and so in one preparation, after the pentachloride and acid had reacted, a small amount of the mixture was poured into water. This caused a decomposition of the phosphorous oxychloride, the para nitro benzoyl chloride remaining as a yellow solid on cooling. The product was purified by recrystallization from ligroin.

The best method finally worked out was: Thoroughly dry and powder the para nitro benzoic acid and put into a large flask. Pulverize the theoretical amount of phosphorous pentachloride and add, with shaking or stirring, to the acid. After a short time the mixture will react and evolve hydrochloric acid. Allow to stand until the reaction slows down, and then heat on the water-bath for an hour. Pour the molten mixture into four times

its volume of water. Do not allow the water to get too hot from the reaction. The phosphorous oxychloride and any excess of phosphorous pentachloride will be decomposed, and the para nitro benzoyl chloride will solidify on cooling. Recrystallize from ligroin. Yield, 85-90%. Forms yellow needles, M.P. 72°C. Two important points in the preparation are: the para nitro benzoic acid must be very dry, and, the phosphorous pentachloride must be well pulverized or charring will take place.

V. Summary and Conclusions.

Of the methods available for the preparation of the compounds made, the esterification of para nitro benzoic acid and subsequent reduction with powdered iron was considered the most satisfactory and was the method used in all syntheses.

The direct esterification of the alcohol and acid with hydrochloric acid as catalyst is the most practical in the case of low molecular weight alcohols when plenty of alcohol is available. The yields by this method are 90-95%. In the case of the higher alcohols esterification is best made by use of para nitro benzoyl chloride with the alcohol. In this case a large excess of the alcohol is not necessary making the method valuable in the case of costly alcohols. The yields will be as high as 90-97%, based on the alcohol used.

The reduction of the nitro compounds with iron powder, using a little hydrochloric acid as starter and catalyst, was found to be very satisfactory in all cases. The reduction of the esters of the higher alcohols goes better if a little alcohol is added to the mixture to increase the solubility. A large excess of iron over the theoretical ammount is necessary, but too large an excess will lessen the yield and cause more trouble.

The anaesthetic properties of the esters do not increase directly with the series but according to my

determinations the amyl ester has the strongest action of all those studied. The conclusion of Stürmers and Lüders[18] that the normal propyl ester was the strongest was probably correct for the esters which they had to investigate. The normal amyl ester was not included in their list. I found as they did[18] that the isoamyl ester acted strongly but was irritating and left unpleasant after-effects. It was supposed that it would prove toxic. The normal amyl ester has even stronger anaesthetic action and acts very mildly until the anaesthesia is noticed. After it is removed from the tongue for a few minutes the feeling is normal again.

Since the normal amyl ester seemed best it was tried on a small cut in my thumb. The pain was practically stopped. The ester seemed to have the effect also of causing the cut to heal quickly. The ester was also administered to a painful ingrown toe nail with the help of a little alcohol. After getting the ester into the painful part the patient reported that the sore part was no longer painful when pricked with a steel point. This suggests the possibility of using this anaesthetic in operations of this kind.

To show the physical and anaesthetic properties of the members of the series as one progresses from the esters of the lower alcohols to those of higher molecular

weight, the following table was prepared. To show the relation to the esters of para nitro benzoic acid a parallel column is included giving the properties of the latter.

	Esters of Para Nitro Benzoic Acid		Esters of Para Amino Benzoic Acid					
	Constants		Formula	Molecular Weight	Melting Point		Solubility	Anaesthetic Strength*
Alcohol Group	M.P.	B.P.			Given	Found		
H (acid)	238	—	$NH_2C_6H_4CO_2H$	137	186-7	—	v.sl. soluble	
Methyl	95-96	—	$C_8H_9O_2N$	151	112	111	sl. soluble	(5)
Ethyl	57	—	$C_9H_{11}O_2N$	165	89-90	—	"	(4)(Mild)
N-Propyl			$C_{10}H_{13}O_2N$	179	73-4		insoluble	(3) Strongly
Isopropyl	111	200 (50 mm)	$C_{10}H_{13}O_2N$	179	85-6	82-3	"	(6) weakly.
N-Butyl			$C_{11}H_{15}O_2N$	193	—		"	
Isobutyl		203 (15 mm)	"	193	65	55-6		
Sec. Butyl			"	193	—			
Tert. Butyl			"	193	—			
N-Amyl		234 (45 mm)	$C_{12}H_{17}O_2N$	207	—	52-3	sol. Alcohol	(1) Strongly (Mild)
Iso Amyl	12	219 (20 mm)	$C_{12}H_{17}O_2N$	207	—	51-2	insoluble	(2)(Harsh)

*Anaesthetic Strength as determined by author.

Figures in red are determinations by author.

The table shows that the melting-point of the esters of para amino benzoic acid lowers with increase of carbon atoms in the esterifying group. The same is true, with some exceptions of the esters of para nitro benzoic acid. The lowest ester of the amino acid, that with methyl alcohol is a solid melting at 112°C, the melting-points ranging down to the isoamyl ester which melts at 52°C. The range of melting-points is greater for the esters of para nitro benzoic acid, dropping from 93°C for the methyl ester to below zero for the normal amyl ester which is still a liquid at -5°C.

In all cases except the isopropyl ester, the amine melts 25-50 degrees higher than the corresponding nitro compound.

In the cases of the esters of the propyl, amyl, (and butyl?) alcohols, the ester of the iso- alcohol has a higher melting point than that of the normal-. with the para nitro benzoic acid. With the amino acid the opposite is the case, the esters of the normal alcohols melting a few degrees higher. Again, the isopropyl ester is an exception to the rule.

VI. Bibliography.

Books.

(1) Corning, J. Leonard — Local Anaesthesia
Appleton and Co. (1886)

(2) Fränkel, Sigmund — Arzneimittel-Synthese
Julius Springer, Berlin (1906)

(3) Knapp, H. — Cocaine and its Uses in Surgery
Putnam's Sons, N. Y. (1885)

(4) Speigel, Leopold
translated by
Leudking and Boylstar — Chemical Constitution and
Physiological Action
D. Van Nostrand & Co.N.Y.(1915)

(5) Beilstein — Handbuch der Chemie
Leopold Voss, Hamburg. (1901)

Papers in Periodicals and Journals.

(7) Beggs, Dr. Herman M. — J. Amer. Med. Assoc.
;176; Ja. 17,(1885)

(8) Clark — J. A. C. S.
30;1149

(9) Einhorn and Heintz — Münch. Med. Wochschr.
44;931 (1897)

(10) Einhorn and Seuffert — Ber.
43;2995-3001 (1910)

(11) Einhorn and Oppenheimer — Ann.
311;158 (1910)

(12) Erdman — Ber.
32;1215 (1899)

(13) Limpricht and Sarr — Ann. 303;278 (1899)

(14) Norris and Green — Amer. Ch. Jour. 26;305

(15) Impens — Therap. Gegenw. 51;348

(16) Rissert — Pharm. Ztg. 47;356 (1902)

(17) Salowski — Ber. 28;1921 (1895)

(18) Stürmers and Lüders — Deut. Med. Wochschr. 34;2310 (1908)

(19) Vorlanders and F.Meyer — Ann. 320;135 (1902)

Patents.

(20) D. R. P. 213 459

(21) D. R. P. 211 801

(22) Brit. Pat. 4 321(21)

(23) D. R. P. 218 389

(24) U. S. A. P. 958 110(23)

(25) Brit.Pat. 17 928(23)

Acknowledgment

The author wishes to express his appreciation of the help that Dr. Roger Adams has been, under whom this work has been done. This problem, selected by Dr. Adams has proven very profitable and interesting and his attentive help has been of great assistance. His personality has been a constant inspiration for me.

Thanks are due to Mr. W. E. Baus for his assistance in the work by making the esters of isobutyl alcohol.

In testing the anaesthetic value of the normal amyl ester of para amino benzoic acid, Mr. G. D. Bauersachs kindly consented to an experiment on himself and reported the action of the compound.

UNIVERSITY OF ILLINOIS-URBANA
3 0112 086765812